November 27, 1992

GUIDANCE[1]

ALPRAZOLAM TABLETS

IN VIVO BIOEQUIVALENCE

AND *IN VITRO* DISSOLUTION TESTING

I. INTRODUCTION

A. Clinical Usage/Pharmacology

Alprazolam is widely used in the management of anxiety disorders (1), panic disorder (2,3,4), social phobia (5) and depression (1,6). It is a triazolo analog of the 1,4 benzodiazepine class of compounds acting on the central nervous system. The exact mechanism of action of alprazolam is unknown; however, published literature indicates that this class of drugs exerts effects by binding to stereospecific receptors at several sites within the central nervous system (7-10). The drug effect is dose-related. The daily dose of alprazolam depends on the individual patient, and averages 1.5 to 4 mg. Although a major metabolite, α-hydroxyalprazolam, shows some pharmacological activity, no alprazolam metabolites possess any clinically important role, and they do not accumulate to any significant degree (11).
Alprazolam is currently available as Xanax ^{R} (Upjohn) in 0.25, 0.5, 1.0 mg and 2.0 mg tablets for oral administration.

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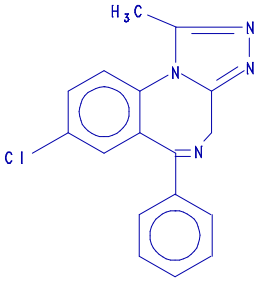
[1] This statement, prepared by the Division of Bioequivalence in the Office of Generic Drugs, is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research, Food and Drug Administration, to the views expressed. For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (Phone: 301-295-8290; Fax: 301-295-8183).

B. Chemistry

The chemical structure of Alprazolam appears in the following figure:



ALPRAZOLAM

Alprazolam is a white crystalline powder insoluble in water but soluble in methanol and ethanol.

C. Pharmacokinetics

Alprazolam is readily absorbed (more than 90%) after oral administration and is distributed widely with a volume of distribution of approximately 1 L/kg in healthy men and women (12). Peak concentrations in the plasma occur one to two hours after administration. With doses ranging from 0.5 to 3.0 mg given on an empty stomach, plasma peak levels of 8.0 to 37 ng/mL were observed. The mean plasma elimination half-life of alprazolam has been reported to be about 11.2 hours (range: 6.3 - 26.9 hours) in healthy adults (13). The drug absorption is slower when alprazolam is taken after a meal than on an empty stomach but total absorption is unchanged (13,14).

II. *IN VIVO* BIOEQUIVALENCE STUDIES[2]

A. Product Information

1. FDA Designated Reference Product: Xanax [R] (Upjohn) 1 mg tablets.

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[2] The sponsoring firm is advised that an Investigational New Drug (IND) application may be required if dosing levels exceed those recommended in the official labeling. See Policy and Procedure Guide 36-92, "Submission of an "Investigational New Drug Application" To the Office of Generic Drugs (OGD)" and 21 CFR 312.2 and 320.31(b)(1).

2. Batch size: The test batch or lot must be manufactured under production conditions and must be of a size at least 10% that of the largest lot planned for full production or a minimum of 100,000 units, whichever is larger.

3. Potency: The assayed potency of the reference product should not differ from that of the test product by more than 5%.

B. Type of Study Required

A single-dose, randomized, fasting, two-period, two-treatment, two-sequence crossover study comparing equal doses of the test and reference products.

C. Recommended Protocol for Conducting a Single Dose Bioequivalence Study under Fasting Conditions.

Objective: To compare the rate and extent of absorption of a generic formulation with that of a reference formulation when given as equal labeled doses.

Design: The study design is a single dose, two-treatment, two-period, two-sequence crossover with a one-week washout period between Phase I and Phase II dosing. Equal numbers of subjects should be randomly assigned to the two possible dosing sequences. Before the study begins, the proposed protocol should be approved by an Institutional Review Board.

Facilities: The clinical and analytical laboratories used for the study should be identified along with the names, titles and curriculum vitae of the medical and scientific/analytical directors.

Selection of Subjects: The number of subjects enrolled in the study should be sufficient to ensure adequate statistical results. It is recommended that a minimum of 24 subjects be used in this study. Subjects should be healthy male volunteers aged 18 to 50 years and within 10% of ideal body weight for height and build (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Subjects should be selected on the basis of acceptable medical history, physical examination, and clinical testing. Subjects with any current or past medical condition which might

significantly affect their pharmacokinetic or pharmacodynamic response to the administered drug should be excluded from the study. Written, informed consent must be obtained from all study participants before they are accepted into the study.

Procedures: Following an overnight fast of at least 10 hours, subjects should be administered a single dose of the test or reference product with 240 ml of water.

Restrictions: Study volunteers should be subject to the following restrictions:

a. Water may be allowed except for one hour before and after drug administration when no liquid should be permitted other than that needed for drug dosing.

b. Subjects should fast for at least four hours after administration of the test or reference treatment. All meals should be standardized during the study.

c. No alcohol or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

d. Subjects should take no Rx or OTC medications beginning two weeks before drug administration until after the study is completed.

Blood Sampling: Venous blood samples should be collected pre-dose (0 hours) and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 24, 36, 48, and 72 hours post-dose. Plasma should be separated promptly and immediately frozen until assayed. Following at least a one-week washout period, subjects should begin the second phase of the study.

Analytical Methods: Alprazolam should be assayed using a suitable method fully validated with respect to adequate sensitivity, specificity, linearity, recovery, accuracy and precision (both within and between days). Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. Chromatograms of the analysis of the unknown samples, including all associated standard curve and quality control

chromatograms, should be submitted for one-fifth of the subjects, chosen at random. The sponsor should justify the rejection of any analytical data and provide a rationale for selection of the reported values.

Statistical Analysis of Pharmacokinetic Data (Plasma): See Division of Bioequivalence Guidance, "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design."

Clinical Report and Adverse Reactions: Subject medical histories, physical examination reports and all incidents of possible adverse reactions to the study formulations should be reported.

III. *IN VITRO* TESTING REQUIREMENTS

A. Dissolution Testing

Conduct dissolution testing on 12 dosage units of the test product versus 12 units of the reference product. The biostudy lots should be used for those product strengths tested *in vivo*. The current official USP dissolution method should be followed and should be referenced by the sponsor. The following USP XXII method (15) and tolerances are currently recommended for this product:

Apparatus:	USP XXII apparatus I (Basket)
RPM:	100 RPM
Medium:	Phosphate buffer solution (pH 6.0) at 37 °C
Volume:	500 mL
Sampling Times:	10, 20, 30 and 45 minutes
Tolerance (Q):	NLT 80% in 30 minutes
Analytical:	As per USP XXII, if available, or other validated method

The percent of label claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

B. Content Uniformity Test

Content uniformity testing on the test product lots should be performed as described in USP XXII.

IV. WAIVER REQUIREMENTS

Waiver of *in vivo* bioequivalence study requirements for the 0.25 mg, 0.5 mg and 2 mg strengths of the generic product may be granted pursuant to 21 CFR 320.22(d)(2) provided the following conditions are met:

A. The 0.25 mg, 0.5 mg and 2.0 mg strengths are formulated proportionally in both active and inactive ingredients to another strength (1 mg) which has demonstrated bioequivalence to a reference (1 mg) product *in vivo.*

B. The 0.25 mg, 0.5 mg and 2 mg strengths of the generic product meet the specified dissolution and content uniformity testing requirements.

C. The drug product follows linear kinetics over its range of available strengths.

V. REFERENCES

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